PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The SecurAstaP trial: Securement with SecurAcath® versus StatLock® for Peripherally Inserted Central Catheters, a randomized open trial
AUTHORS	Goossens, GA; Grumiaux, Niel; Janssens, Christel; Jérôme, Martine; Fieuws, Steffen; Moons, Philip; Stas, Marguerite; Maleux, Geert

VERSION 1 – REVIEW

REVIEWER	Claire Rickard Griffith University Australia
REVIEW RETURNED	24-Feb-2017

GENERAL COMMENTS	There are no randomised controlled trials to date on this topic and so this paper provides welcome evidence and will be very helpful to clinicians, patients and policy makers. Millions of PICCs are used worldwide, with numerous options for securement and little evidence to guide practice. Further PICC complications and failure are very common so these sort of studies are urgently needed. I note that there is no manufacturer funding declared which reasssures no bias was at play from this perspective. The trial was prospectively registered on the trials registry with consistent endpoints, this supports rigor. Most aspects of RCT design appear to have been undertaken with high quality and in line with expected standards. A few suggestions to make the paper clearer: 1. State which transparent dressing was used in both groups, since this is an important aspect of readers understanding the generalisability of results to their setting 2. briefly state if the allocation concealment method was maintained (i.e. did the opaque numbered envelope approach have any problems. 3. Add brief explanation of how screening and recruitment occurred. 4. Be clear if results are average dressing time per procedure (I think they are) or for the patient's dressings overall (for all of their PICC dressings). If the former, perhaps add a sentence in discussion that the total dressing time saved per patient with statlock was X minutes on average. 4. Were Adverse Events related to each product (MARSI of the product, redness, skin injury, itching etc monitored systematically, or just for some complications such as pain? Consider having a subheading under results that discusses AEs. 5. A picture of each regimen would be helpful, please state if the statlock was used UNDER or OUTSIDE of the transparent dressing.

	The manufacturers recommend UNDER the dressing (i.e. closer to the PICC insertion site) but I see a lot of hospitals placing it outside of the dressing (as they are afraid to dislodge it when changing the dressing, and think they are saving time and money by doing this since they can change the statlock and dressing independently of each other). 6. As PICCs were in place for different periods, and a complication early e.g. Day 3 is far worse than the same complication occurring later, say on Day 30, consider a time based analysis for your secondary endpoints of complications, or perhaps a kaplan meier survival curve to demonstrate when the failure/premature removal occurred for PICCs with complications. I note your median dwell was shorter (16 days) with statlock than securacath (21 days) which does raise the question if complications occurred sooner with statlock. Consider whether this should be reported/analysed even though the same overall percentage of complications was the same between groups. Incidence per 1000 catheter days would also be a good way to compare risk between groups that accounts for the different dwell times both within and between groups. 7. The higher drop out rate in the Statlock group (10/53 vs 3/52) needs more justification so that readers are assured that this in no way introduced attrition bias. For example 2 statlock patients are excluded as they died (according to Fig 1). This ~20% attrition in the Statlock group will cause readers to question the results. Why is death a reason for exclusion? I also note that in the study overall, 8 patients died (Table 4), so this raises the question of why the 2 were excluded for death in the statlock group. 2 patients are said to be excluded for 'logistic reasons' in the statlock group, this also needs further explanation. Furterm in the study (Fig 1) 6 patients are excluded as dwell is "too short" - this needs to be defined in the methods. Even if these patients had no dressing timing for the primary endpoint, they should still be included in the analysis for secondary endpoints of PICC complications.. For example if they were removed due to dislodgement on Day 3, they may never have needed a dressing replacement on Day 7, yet their dislodgement could be caused by their securement method. I suggest that you include as many as possible in the final analysis, and if there is missing data for the primary endpoint, you can note that for that analysis, yet still include them in the other endpoints. In Table 4 it says one patient withdrew - can you provide a reason to this, is it related to complications with the product or completely unrelated? 8. Abstract "180 days follow" should be "180 days follow-up". Last sentence of results (in abstract) needs rewording as a bit unclear) 9. Discussion - was it the same subset of securacath patients who had moderate-severe pain at each of insertion-dwell and removal? 10. Is the MARSI in Table 3 related to the statlock or to the transparent dressing? 11. Table 4 - suggest add a row displaying the total number per group removed for complications (since the other rows are not mutually exclusive i.e. patients could have more than one complication). 12. p.16 please add the % to the 15 cases of difficulty removing securacath

REVIEWER	Robert B Dawson Acute Care Hospitalist, Nurse Practitioner New England Inpatient Specialist Vascular Access Specialist / Consultant Vascular Access Consultants, LLC USA
REVIEW RETURNED	03-Jun-2017

GENERAL COMMENTS	Thank you for this most interesting study in an area of great need, i.e. time for care and maintenance. Unfortunately, no economic impact was presented, but with the data provided some post study analysis is certainly possible by interested parties. Some comments for consideration: 1. The training or rather competence of clinicians was set at measuring experience level with a specific device. Authors account for this in terms of pain experienced with subcutaneous device removal. It would have been more methodologically sound to provide a specific competency period with formal training on IFUs, then followed by an experience measure. Without specific standardized training and competency it is hard to interpret the cause of statistically significant higher pain scores with a presumed more technical device. A reader may assume a training issue, but the lack of addressing training and competency leaves this to question further. (I would advise adding more detail on this issue, or at least address in limitations) 2. The measure of migration, defined as external length > or = 3cm. I think this needs to be explained further. Why was this used to define migration. I would consider the fact that any catheter movement could contribute to complication of thrombosis and infection. Therefore, visible/ measurable migration should have been recorded and reported as part of results. Anything, verifiable, would be 1cm or more in my opinion given the standard graduating markings. Thought given the lack of statistical significance with complications i.e. CRBSI this would not be a completed methodological concern. (I would like authors to address the reason / rationale for 3cm or greater migration definition) 3. It would have been interesting to note, how many actual dressing changes occurred per 7 day period for each device group. Again, the number of dressings beyond 1 per 7 days would be something that adds to time concerns, but also inherent risk for complications related to disturbing the catheter - skin junction. Thank you again for this most interesting and well written paper.

REVIEWER	Dr Irina Chis Ster St George's University of London
REVIEW RETURNED	16-Jun-2017

GENERAL COMMENTS	I am a statistical epidemiologist by training and experience and hence my review refers to these particular aspects of the paper. May I emphasize that the clinical sides of the paper are beyond my expertise and I am unable to critically evaluate the devices or the clinical procedures. Whist correct in principle (mixed linear models on the log transformed outcome) I would like to invite the authors to revise both

	the analysis and clarify the data presentation. Specifics are elaborated below. 1. “The most frequent indication for PICC insertion was the administration of intravenous antibiotic therapy” - are the proportions in the groups balanced regarding this recommendation? 2. Is the experience of the specialized staff (i.e. 0, <10 and >10) equally balanced across experimental groups? 3. Judging upon the flow diagram presented on page 10, the loss at the follow up is statistically different amongst groups: 10/53=18.9% in one group and 3/52=5.8% (p=0.04) 4. It is unclear from the paper which are the numbers in each group the statistics for the main outcome rely upon. Looking into table 4 - I understand that the analysis is carried on 31 and 35 patients respectively? Can the authors quantify how much in loss of power is compensated by multiple measurements per individual? 5. Table 1 does a poor job in presenting the data. I would expect some baseline comparisons between groups to check whether the randomisation produced balance groups regarding all aspects apart from intervention. 6. Table 2: why do the authors report odd ratios? I can see percentages % less than 1, the assumptions no longer hold and the CIs are massive. There are many reports on p-value of 1. That might be down to software setting for reporting the decimal numbers but the authors should know that there is no such thing as p-values of 1 or 0. Fisher’s exact tests should be used for cross tabulated categorical data with small numbers in a cell. One reports a p-value>0.99 if the software displays the value of 1… 7. The number of dressing changes is inappropriately reported using means and standard deviations (page 11) – this is a count, the median and IQR are more appropriate than mean/sd. To not say that their distribution is obviously rightly skewed. 8. Table 3 and 4 are also flawed. The last two mention that the OR are not determined and yet presenting CIs for ORs. Whilst some aspects of these data may be of clinical interest, statistics are all about the uncertainty. In the absence of the necessary numbers to work it out, one just need to comment on clinical aspects of a finding. Those infinite CIs do not make sense. 9. Patients were followed for a total of 3113 days (page 9) – I would not say that this is a relevant statistic.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Claire Rickard
A few suggestions to make the paper clearer:
1. State which transparent dressing was used in both groups, since this is an important aspect of readers understanding the generalisability of results to their setting

Response: We are grateful for that suggestion and added the following to the section “Outcomes and procedures”
In both groups similar types of catheter dressing were used. At insertion, a gauze dressing, (Cosmopor® E, Hartmann) which has to be changed within 24 hours, was applied thereafter a transparent semipermeable membrane (TSM) dressing (TegadermTM 3M) was used. The TSM dressing was always placed over the securement device (Figure 1 and 2). In case of signs of exit site

infection, a Biopatch® (Johnson & Johnson) was applied. CavilonTM(3M) was used in case of skin irritation.

2. briefly state if the allocation concealment method was maintained (i.e. did the opaque numbered envelope approach have any problems.

Response: We understand that the information will be more completely and therefore we added the following sentence to the section “Outcomes and procedures”
The allocation concealment method was maintained, without problem.

3. Add brief explanation of how screening and recruitment occurred.

Response: We agreed that the screening and recruitment could be reported more detailed therefore we added the following to the section “Study design”
All patients scheduled for PICC insertion in the IR suite were screened by a member of the research team for eligibility. Patients were recruited by the same team at a hospital ward or in rare occasions in the waiting room of the IR suite.

4.a Be clear if results are average dressing time per procedure (I think they are) or for the patient's dressings overall (for all of their PICC dressings). If the former, perhaps add a sentence in discussion that the total dressing time saved per patient with statlock was X minutes on average.

Response: We suppose you meant “that the total dressing time saved per patient with SecurAcath®…”
We thank you for this important remark because this was not formulated clear. Indeed, the reported differences in time for dressing change are “average dressing time per procedure” and more precisely the average that is reported is the geometric mean. So, we added the following to “Result section”
In the StatLock® group, the geometric mean time needed per dressing change (Statlock® change included) was 7.3 minutes (95% CI 6.4 – 8.3) and in the SecurAcath® group 4.3 minutes (95% CI 3.8 – 4.9) (P <0.001).

With 3 minutes time saved per dressing change and on average 3.4 dressing changes per patient this resulted in 10 minutes time saved per patient.

However, since the number of dressing changes is highly variable per patient and the true number of dressing changes per patient is not known because some dressing change measurements are missing (nurses forgot sometimes to do the measurement) and therefore underestimated. We deemed it was more appropriate to focus on the time saved per dressing change and not on the time saved per patient. Therefore we added to the “Discussion section” the following:
Indeed, we found a mean reduction in time of 3 minutes per dressing change procedure in the SecurAcath® group compared to the StatLock® group (P< 0.001).

4.b Were Adverse Events related to each product (MARSI of the product, redness, skin injury, itching etc monitored systematically, or just for some complications such as pain? Consider having a subheading under results that discusses AEs.

Response: At each dressing change, pain, catheter migration, MARSI and infection signs at exit site were recorded systematically. Additionally, other AEs could be noted down on the dressing change study form. Note that these AEs only were recorded at dressing change and not on a continuous basis and therefore the incidence numbers were in both groups underestimated.

Therefore we restructured the “Result section” and we’ve made a subheading Adverse Events.

Table 3 summarizes the adverse events reported during dressing change. No adverse events were reported during dressing changes in 61.5% in the StatLock® group and in 65,9% in the SecurAcath® group. Both groups were comparable regarding the number of adverse event reports (P=0.41). Clinical signs of bleeding, oozing or a haematoma at the exit site were reported in 13% and 13.6% of dressing changes in the StatLock® group and SecurAcath® group, respectively (P=0.68). Explicitly pain reports without mentioning any other complication were similar in both groups (P=0.90). Medical Adhesive-related Skin Injury (MARSI) was reported comparable in both groups (P=0.80).

We appreciate your remark regarding MARSI and we explicitly added to the “Discussion section” that MARSI was unrelated to both of the securement devices.
We found no statistical significant difference between MARSI in the StatLock® (3.7%) and SecurAcath® (4.3%) group (P=0.80). Moreover it was explicitly documented in 74% of cases that the MARSI was observed along the TSM dressing surface and no indication was found to MARSI limited to neither the StatLock® nor the SecurAcath® zone. Therefore we conclude that MARSI is a minor adverse event unrelated to both types of securement device.

5. A picture of each regimen would be helpful, please state if the statlock was used UNDER or OUTSIDE of the transparent dressing. The manufacturers recommend UNDER the dressing (i.e. closer to the PICC insertion site) but I see a lot of hospitals placing it outside of the dressing (as they are afraid to dislodge it when changing the dressing, and think they are saving time and money by doing this since they can change the statlock and dressing independently of each other).

Response: We understand that pictures of both devices with the catheter dressing in place will enhance clarity and therefore we added the two figures and referenced to it in the “Outcome and procedures” section.
Figure 1 PICC with SecurAcath®
Figure 2 PICC with StatLock®

We explicitly added the following to the “Outcomes and procedures” section:
The TSM dressing was always placed over the securement device (Figures 1 and 2).

6. As PICCs were in place for different periods, and a complication early e.g. Day 3 is far worse than the same complication occurring later, say on Day 30, consider a time based analysis for your secondary endpoints of complications, or perhaps a kaplan meier survival curve to demonstrate when the failure/premature removal occurred for PICCs with complications. I note your median dwell was shorter (16 days) with statlock than securacath (21 days) which does raise the question if complications occurred sooner with statlock. Consider whether this should be reported/analysed even though the same overall percentage of complications was the same between groups.
Incidence per 1000 catheter days would also be a good way to compare risk between groups that accounts for the different dwell times both within and between groups.

Response: We agree totally with this remark though the incidence numbers of the secondary outcomes are extremely small. Therefore we refrained for reporting results from survival analyses (e.g. Kaplan Meier analyses) . The incidence numbers on the adverse events (complications) were only recorded when observed during dressing change and therefore underestimated and the exact date of occurrence might be flawed.

We understood the reviewer’s concern and we added the day of occurrence when referring to table 2 (secondary outcomes).

They reported 2 cases of an external catheter part of ≥3 cm: 4 cm (n=1) the second day after PICC placement in the StatLock® group versus 20 cm (n=1) on the day after PICC placement in the SecurAcath® group (P= 1.00).

7. The higher drop out rate in the Statlock group (10/53 vs 3/52) needs more justification so that readers are assured that this in no way introduced attrition bias. For example 2 statlock patients are excluded as they died (according to Fig 1). This ~20% attrition in the Statlock group will cause readers to question the results. Why is death a reason for exclusion?
I also note that in the study overall, 8 patients died (Table 4), so this raises the question of why the 2 were excluded for death in the statlock group. 2 patients are said to be excluded for 'logistic reasons' in the statlock group, this also needs further explanation. Furterm in the study (Fig 1) 6 patients are excluded as dwell is "too short" - this needs to be defined in the methods. Even if these patients had no dressing timing for the primary endpoint, they should still be included in the analysis for secondary endpoints of PICC complications.. For example if they were removed due to dislodgement on Day 3, they may never have needed a dressing replacement on Day 7, yet their dislodgement could be caused by their securement method. I suggest that you include as many as possible in the final analysis, and if there is missing data for the primary endpoint, you can note that for that analysis, yet still include them in the other endpoints.

Response: We totally agree that the flow diagram cause confusion. The flow diagram as displayed showed the participant flow for the analysis of the primary outcome, however, all available data on 51 patients in both groups were used in the final analysis.
We updated the flow diagram showing that there was no loss to follow-up but that we missed data on the time measurements for the primary outcome. We tried to be more explicit regarding the reasons for the patient exclusions and changed the ‘logistic reasons’ into ‘nurses forgot to measure”. Also the too short time period is reported more detailed to show that PICCs were removed or patients die within a couple of days after PICC placement.

We updated the flow diagram providing more details on the patient flow. We added the following to the “Result section”:
PICC insertion was cancelled in three patients. No patients were lost to follow up. No reports of measurements of the dressing change procedure were available for 10 patients, 8 in the StatLock® and 2 in the SecurAcath®. group. The main reason for the missing data was the short period of time that the PICC was in place. Figure 3 shows the patient’s flow .

In Table 4 it says one patient withdrew - can you provide a reason to this, is it related to complications with the product or completely unrelated?

It was completely unrelated, however the patient’s condition was worsening.
A footnote was added to Table 4:
Unrelated to the securement device use

8. Abstract "180 days follow" should be "180 days follow-up".

Response: Corrected in abstract

Comment: Last sentence of results (in abstract) needs rewording as a bit unclear) The user-friendliness at insertion and removal was scored significantly higher for StatLock® than for SecurAcath® ($P<0.05$), except for the statement regarding to use the device routinely, at removal, where no difference was found between the two devices ($P=0.32$).

Response: We understand that this sentence need rewording. We adapted the sentence in the abstract as follows:
The user-friendliness was scored at insertion and removal. All statements regarding the user-friendliness at insertion and removal were scored significantly higher for StatLock® than for SecurAcath® ($P<0.05$). Only for the statement regarding the routine use of the device, which was asked at removal, no difference was found between the two devices ($P=0.32$).

We realised that the results on the user-friendliness could be improved in the "Results section". We reworded in the "Result section" as follows:
Overall, the usability of StatLock® was evaluated statistically significantly more positive than SecurAcath® at insertion and removal.

9. Discussion - was it the same subset of securacath patients who had moderate-severe pain at each of insertion-dwell and removal?

Response: The specific scores of the three patients with moderate/severe pain at insertion are given in the table below.

	Insertion N=49	Dwell N=41	Removal N=44
Patient 83	4	0	4
Patient 16	6	No data	No data
Patient 64	7	0	4

Although, the numbers of patients with moderate/severe pain at insertion are low, we looked at the relation of the NRS scores between the pain at insertion and pain during dwell time (Spearman rho =-0.064, P =0 .69) and between the pain at insertion and pain during removal (Spearman rho = 0.316, P = 0.04).

We added this information to the "Result section" as follows:
In the SecurAcath® group, pain at insertion and pain during dwell time were not related (Spearman rho = - 0.064, P =0 .69. Pain at insertion and at removal were statistically significantly related (Spearman rho = 0.316, P = 0.04).

Comment: During this new analysis we found 3 cases with a NRS score of "0" in the Securacath® group that were accidentally wrongly coded as "missing data" instead of "none". The number of patients which reported "0" was 20 instead of 17. The result of the statistical test for difference in pain reporting between the two groups remained statistically significant.

Response: We corrected this information in "Table 2 "as follows:
We changed "17" with "none" reported pain into "20" and updated the percentages in Table 2.

10. Is the MARSI in Table 3 related to the statlock or to the transparent dressing?

Response: For this important remark we refer to our comments about MARSI under 4b. above.

11. Table 4 - suggest add a row displaying the total number per group removed for complications (since the other rows are not mutually exclusive i.e. patients could have more than one complication).

Response: In our study we found only one complication as reason per patient (or confirmed CRBSI, or suspected CRBSI, or dislodgement, or catheter malfunction) for PICC removal. All patients with a CRBSI complication as reason for removal of their catheter haven't a problem of catheter

dislodgement nor have a catheter malfunction. We understand that the table could suggest mutual exclusivity. Therefore we adapted the explanation about the “end of study reasons” and reorganised Table4 to increase the readability. We removed the subheading “Complications” and made 2 new headings: (1) Patients with removed PICCs at the end of the study (5 patients in each group) and (2) Patients with their PICC in situ. Table 4 present the reasons for the end of study, In 4 patients in 51 patients in the StatLock® group we couldn’t find back the reasons for removal. Percentages were accidently wrongly calculated on 51 patients instead of 47patients. We corrected for this mistake. No change in statistical difference between the groups were found. We added a sentence to draw the attention to the fact that in 4 cases in the StatLock® group the end of study reason was unknown. We adapted Table 2 and 4 accordingly and text in the “Result” section as follows:

The reasons for the end of study were listed in table 4. PICCs were prematurely removed due to one specific complication in 21.3% of cases (n=10) in the StatLock® group and in 21.6% of cases (n=11) in the SecurAcath® group. In 4 cases in the StatLock® group the reason for removal was unknown.

12. p.16 please add the % to the 15 cases of difficulty removing securacath

Response: We added the % to p16:
15 in 44 cases= 34%

Reviewer 2
1. The training or rather competence of clinicians was set at measuring experience level with a specific device. Authors account for this in terms of pain experienced with subcutaneous device removal. It would have been more methodologically sound to provide a specific competency period with formal training on IFUs, then followed by an experience measure. Without specific standardized training and competency it is hard to interpret the cause of statistically significant higher pain scores with a presumed more technical device. A reader may assume a training issue, but the lack of addressing training and competency leaves this to question further. (I would advise adding more detail on this issue, or at least address in limitations)

Response: We totally agree with the reviewer that training and competence acquisition is a major issue in the use of SecurAcath®. To anticipate for this issue, along the study protocol, only APN from the Vascular access team would remove the SecurAcath®. These APN were formally trained 6 months before study start during the initiation of the use of SecurAcath® in our hospital. We used SecurAcath® in 70 patients which allowed for training on insertion by the radiologists, care by the nurses and removal of the device by the APN of the vascular access team.
Actually, a minority of PICCs with SecurAcath® (n=7) were removed by clinicians without any experience with the device instead of the trained APN.
To clarify this important issue we added more information on the training in the methodology section.

Moreover we took a closer look at the pain scores with SecurAcath® at removal in relation to the experience of the clinician. Post-hoc analysis found no difference in pain scores as a function of the experience of the clinician within the SecurAcath® group. We added this information to the discussion section

The following has been added to “Materials and methods” section:
At the initiation of SecurAcath® in the hospital, 6 months before study start, inserters followed a formal training on the placement of SecurAcath® and also the APN of the vascular access team were trained for device removal. The first 70 patients with a PICC secured with SecurAcath® were followed closely to monitor problems and complications with the devices, including optimising placement and removal technique. These trained interventional radiologists inserted single lumen Bard PowerPICCs

(C.R. Bard Inc., Salt Lake, UT, USA) and they completed a case report form containing the indication for insertion, PICC details and perioperative problems. The experience of the radiologists who placed and, nurses and physicians who removed the securement device, was assessed on a categorical level (no experience, < 10 and ≥ 10 times). APN from the vascular access team removed the SecurAcath®.

The following has been added to the “Discussion” section
We observed higher pain scores at removal within the SecurAcath® group. A possible explanation could be that in this group not all devices were removed by the experienced APN from the vascular access team, as intended. However, in a post-hoc analysis we found no difference in pain scores as a function of the experience of the clinician within the SecurAcath® group.

2. The measure of migration, defined as external length > or = 3cm. I think this needs to be explained further. Why was this used to define migration. I would consider the fact that any catheter movement could contribute to complication of thrombosis and infection. Therefore, visible/ measurable migration should have been recorded and reported as part of results. Anything, verifiable, would be 1cm or more in my opinion given the standard graduating markings. Thought given the lack of statistical significance with complications i.e. CRBSI this would not be a completed methodological concern. (I would like authors to address the reason / rationale for 3cm or greater migration definition)

Response: We defined migration as a 3 cm supplementary external movement of the catheter because this is a substantial slip out of the catheter, which could lead to loss of venous access.

We understand the reviewers’ concern and added the differences between the reported catheter length at insertion and at dressing change. We found a mean difference in length of 0.2 cm (SD 0.8 cm) in the StatLock® group and a mean difference in length of 0.1cm (SD 2.0 cm) in the SecurAcath® group.

We added the following to the “Outcomes and procedures” section
We opt to define migration as a 3 cm supplementary external movement of the catheter because this is a substantial slip out of the catheter which could lead to loss of venous access.

We added the following to Table 1
Mean (SD) and minimum and maximum difference in reported catheter length at dressing change compared to insertion were added to Table 1.

3. It would have been interesting to note, how many actual dressing changes occurred per 7 day period for each device group. Again, the number of dressings beyond 1 per 7 days would be something that adds to time concerns, but also inherent risk for complications related to disturbing the catheter - skin junction.

Response: We agree with the reviewer that this information is valuable and therefore we added the information added in the results section. Note however that these numbers are likely to be underestimated since not all dressing changes are recorded in both groups.

The following was added to the “Results” section
Both groups were comparable regarding the number of days between reported dressing changes. The mean number of days between dressing changes was 6.8 (SD 6.0) in the StatLock® group and 7.0 (SD 7.5) in the SecurAcath® group.

Reviewer 3

1. “The most frequent indication for PICC insertion was the administration of intravenous antibiotic therapy” -are the proportions in the groups balanced regarding this recommendation?

Response: From a clinical point of view, both groups are balanced. Note that we deliberately do not report P-values comparing both groups since this is an inappropriate practise in RCTs (see for example Knol et al. 2012).

Knol MJ, Groenwold RH, Grobbee DE. P-values in baseline tables of randomised controlled trials are inappropriate but still common in high impact journals. Eur J Prev Cardiol. 2012 Apr;19(2):231-2.

2. Is the experience of the specialized staff (i.e. 0, <10 and >10) equally balanced across experimental groups?

Response: The experience with the securement device at dressing change is lower in the SecurAcath® group, which was expected since this is a new device. However despite this lower degree of experience, we found a shorter dressing change time (primary outcome).

3. Judging upon the flow diagram presented on page 10, the loss at the follow up is statistically different amongst groups: 10/53=18.9% in one group and 3/52=5.8% (p=0.04)

Response: We agree with the reviewer that there is an imbalance, with less patients in the primary outcome analysis sample within the StatLock® group. However, the reasons why these data are missing are unrelated to the primary outcome. All other data were collected and analysed for all patients with a PICC insertion in the study.
We realised that data on the flow chart were confusing because they only reported the number of patients which were analysed for the primary outcome. We adapted the flow chart to make it more accurate.

We updated the flow diagram providing more details on the patient flow.

4. It is unclear from the paper which are the numbers in each group the statistics for the main outcome rely upon. Looking into table 4 - I understand that the analysis is carried on 31 and 35 patients respectively?

Response: The primary analysis was performed on 325 dressing changes from 43 and 49 patients in StatLock® and SecurAcath® groups, respectively. This issue has been clarified in the new version of the flow diagram (which was indeed confusing). We refer to the third comment here above. Table for present the “Reasons for the end of study”.

Can the authors quantify how much in loss of power is compensated by multiple measurements per individual?

The ICC (quantifying the correlation between the multiple dressing change measurements from the same patient) equalled 0.29, which yields a variance inflation factor (design effect) equal to 1+0.29 (3.5-1)=1.725, where 3.5 is the mean number of dressing changes per patient. Applying this inflation factor on the original sample size calculation would require 102*1.725=176 dressing change measurements in total. Hence with a total of 325 dressing change measurements, the desired power level of 80% was largely safeguarded.

We added the following to the “Discussion” section
More specifically, with 3.5 as the mean number of dressing change measurements and 0.29 as the correlation between the multiple dressing change measurements from the same patient, the design effect equaled 1.725. Applying this inflation factor on the original sample size calculation at least 176 (=102*1.725) dressing change measurements in total were required to guarantee the desired power level of 80%.

5. Table 1 does a poor job in presenting the data. I would expect some baseline comparisons between groups to check whether the randomisation produced balance groups regarding all aspects apart from intervention.

Response: We understand the reviewer’s concern, however we refer to our reply on the first comment, where we explained that we deliberately do not report P-values comparing both groups since this is an inappropriate practise in RCTs (see for example Knot et al. 2012).

Knol MJ, Groenwold RH, Grobbee DE. P-values in baseline tables of randomised controlled trials are inappropriate but still common in high impact journals. Eur J Prev Cardiol. 2012 Apr;19(2):231-2.

6. Table 2: why do the authors report odd ratios? I can see percentages % less than 1, the assumptions no longer hold and the CIs are massive. There are many reports on p-value of 1. That might be down to software setting for reporting the decimal numbers but the authors should know that there is no such thing as p-values of 1 or 0. Fisher’s exact tests should be used for cross tabulated categorical data with small numbers in a cell. One reports a pvalue> 0.99 if the software displays the value of 1…

Response: We have removed the effect size from the tables. Results from Fisher’s exact tests were used for all comparisons of proportions (references to Chi^2 were removed). Note however that P-values of an exact test can be equal to 1 since the distribution of the test statistic is discrete. For classical tests though based on a t-distribution, normal distribution,… p-value can indeed not be equal to 1.
We removed also the reference to the Chi^2 test in the statistical analysis section.

7. The number of dressing changes is inappropriately reported using means and standard deviations (page 11) – this is a count, the median and IQR are more appropriate than mean/sd. To not say that their distribution is obviously rightly skewed.

Response: We thank the reviewer for drawing our attention to this.

We added the following to the “Result” section
Time was measured during 325 dressing changes with 161 in the StatLock® group and 164 in the SecurAcath® group with a mean number of 3.74 (SD 3.48) with a median of 3 (Q1 = 2; Q3 = 6) and 3.35 (SD 2.89) with a median of 2 (Q1 = 1; Q3 = 5) measurements per patient, respectively.

8. Table 3 and 4 are also flawed. The last two mention that the OR are not determined and yet presenting Cis for ORs. Whilst some aspects of these data may be of clinical interest, statistics are all about the uncertainty. In the absence of the necessary numbers to work it out, one just need to comment on clinical aspects of a finding. Those infinite CIs do not make sense.

Response: We removed effect sizes from the table 3 and 4.

9. Patients were followed for a total of 3113 days (page 9) – I would not say that this is a relevant statistic.

Response: We removed that sentence.

VERSION 2 – REVIEW

REVIEWER	Dr Claire Rickard Alliance for Vascular Access Teaching and Research, Menzies Health Institute, Griffith University
REVIEW RETURNED	01-Sep-2017

GENERAL COMMENTS	I thank the authors for their commitment and hard work on this revision. The paper is much clearer. The following issues could be considered: 1. I now understand that Fig 3 is only referring to the flow of patients for the primary endpoint. The authors have said they reworded some parts of this, but the older version appears to be uploaded. E.g. the term "logistic reasons" for exclusion was said in the response letter to have been changed to "nurses forgot to measure" however this has not been changed in the version I received. I suggest that the words in Fig 3 "catheter dwell too short" would be more clear if "no dressing changes done". Otherwise there may be a misunderstanding that the authors set a limit on dwell time for analysis. I still am unclear why death is an exclusion in Fig 3 for the primary analysis. If they had a dressing change, and it was timed, then why can't they be included? Or is it because they died before a dressing change occurred? If this is the reason, couldn't they also fit under the reason "no dressing changes done". 2. So I understand from the author's response that the number included for secondary endpoints was 51 per group. This is what I would expect, as even if they died without a dressing change done, it is still relevant and important as to what complications they did or did not have over the period that they were alive. I think this could be clarifed in the first para of "Patient and Device characteristics". Table 4 does not currently show 51 per group. Table 2 has no N at the top of the Securacath/statlock columns, but appears to be only 47 patients in one group, not 51. Could the authors also clarify that they compared 51 per group in the text at the beginning of the section (p.12) "Migration etc" Abstract: I suggest that the last sentence of the results would be clearer if the word" recommending" is inserted i.e. "regarding recommending routine use". Many thanks for the chance to review this important work.

REVIEWER	Dr Irina Chis Ster St George's University of London
REVIEW RETURNED	08-Sep-2017

GENERAL COMMENTS	The authors did not address sufficiently clear the issue of missing data -there is a marginally difference between groups. Some sensitivity analyses to the the findings are certainly required. How much the estimates change if the missing data take some extreme

	values (within data range of course) ? At least some analysis under missing at random (MAR) assumption is required. It shouldn't be much extra work - there is plenty of software with readily available routines for such analyses. The p-values values are 1 only when the distributions of the two samples for instance are identical - I could not see that was the case.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Dr Claire Rickard
Institution and Country: Alliance for Vascular Access Teaching and Research, Menzies Health Institute, Griffith
University Please state any competing interests: Nil

Please leave your comments for the authors below
I thank the authors for their commitment and hard work on this revision. The paper is much clearer. The following issues could be considered:
1. I now understand that Fig 3 is only referring to the flow of patients for the primary endpoint. The authors have said they reworded some parts of this, but the older version appears to be uploaded. E.g. the term "logistic reasons" for exclusion was said in the response letter to have been changed to "nurses forgot to measure" however this has not been changed in the version I received.
I suggest that the words in Fig 3 "catheter dwell too short" would be more clear if "no dressing changes done".
Otherwise there may be a misunderstanding that the authors set a limit on dwell time for analysis.
I still am unclear why death is an exclusion in Fig 3 for the primary analysis. If they had a dressing change, and it was timed, then why can't they be included? Or is it because they died before a dressing change occurred? If this is the reason, couldn't they also fit under the reason "no dressing changes done".

Response: We have to apologize because, indeed, I uploaded the original flow chart instead of the revised one. We added the revised flow diagram and clarified accordingly the text in Figure 3. Indeed in 8 patients (6 in the StatLock® and 2 in the SecurAcath® group), the reason for the missing data was that no dressing changes were done due to the short PICC dwell time because the PICC was removed (accidently or electively) early or in 1 case, the patient died within 3 days post insertion.

2. So I understand from the author's response that the number included for secondary endpoints was 51 per group. This is what I would expect, as even if they died without a dressing change done, it is still relevant and important as to what complications they did or did not have over the period that they were alive. I think this could be clarifed in the first para of "Patient and Device characteristics".

Response: We agree with the reviewer's comment. However missing data were inconstant for all variables. E.g. we miss the reason for PICC removal in 4 cases in the StatLock® group which results in a total number of 47 patients in the StatLock® group versus 51 patients in the SecurAcath® group. And the pain score at removal was reported only in 25 patients in the StatLock® and 44 in the SecurAcath® group. To clarify this issue we added the following in the beginning of "Patient and Device characteristics" section:

For the primary outcome analysis we have data on 43 patients in the StatLock® group and 49 in the SecurAcath® group. For the secondary outcomes, the 51 patients per group were taken into account,

however the completeness of the data is varying along the different variables. Therefore, in the tables, in the corresponding row, the total number of patients and/or measurements is shown per variable.

Comment: Table 4 does not currently show 51 per group.

Response: Indeed as indicated above we miss the reason for PICC removal in 4 cases in the StatLock® group.
However we opt not to take the 4 unknown cases in the calculations in order to avoid potential underreporting of the actual complications at removal. This was described under the section “End of study reasons”. To further clarify this issue, we added in the caption of the table “°in 4 cases the reason for removal was unknown” and we moved the sentence below as second sentence in that section.

Comment: In 4 cases in the StatLock® group the reason for removal was unknown.

Table 2 has no N at the top of the Securacath/statlock columns, but appears to be only 47 patients in one group, not 51.

Response: To avoid confusion we added the total number of patients/measurements for every variable in the corresponding row.

Comment: Could the authors also clarify that they compared 51 per group in the text at the beginning of the section (p.12) "Migration etc"

Response: We added the following to that paragraph to clarify the 47 instead of 51 per group in the StatLock® group:

Comment: The reason for PICC removal is unknown in 4 cases in the StatLock® group. Therefore calculations regarding PICC removal are performed on 47 instead of 51 cases in the StatLock® group.

Response: Furthermore we add in the text the number of cases, i.c. 47 cases (StatLock®) and 51 cases (SecurAcath®), to the number of dislodgements and lab-confirmed CRBSI. Migration was reported on the number of dressing changes which was explained in the text and table already.

3 Abstract: I suggest that the last sentence of the results would be clearer if the word" recommending" is inserted i.e.
"regarding recommending routine use".

Response: We thank the reviewer for this suggestion and we adapted the abstract text accordingly.

Reviewer: 3
Reviewer Name: Dr Irina Chis Ster
Institution and Country: St George's University of London Please state any competing interests: None declared.

Comemnt: The authors did not address sufficiently clear the issue of missing data -there is a marginally difference between groups. Some sensitivity analyses to the findings are certainly required. How much the estimates change if the missing data take some extreme values (within data range of course) ? At least some analysis under missing at random (MAR) assumption is required. It shouldn't be much extra work - there is plenty of software with readily available routines for such analyses.

Response: We are grateful the reviewer for the valuable suggestion to add more information on the potential impact on missing data. We added the following to the discussion section:

We have further clarified the issue of missing data in 3/52 and 10/53 of the patients randomized to the SecurAcath® and StatLock® group, respectively. For 3/52 and 10/53 of the patients randomized to the SecurAcath® and StatLock®) group, respectively, no data were available on the analysis sample. Although not being statistically significant (p=0.073) we have added a sensitivity analysis to study the potential impact on the drawn conclusion for the primary outcome. To obtain a non-statistically significant difference between both groups, the time needed for dressing change for patients with missing data would have been at least 2.8 times longer for the 3 patients in the SecurAcath® group compared to the 10 patients in the StatLock® group. Since this is highly unlikely, we can safely conclude that the obtained finding on the primary outcome is robust with respect to the presence of missing data (Figure 5 Sensitivity analysis in supplementary files).

A supplementary figure with the sensitivity analysis with the following information is added in the supplementary files:

Various scenarios were considered for the randomized patients without any measured time needed for dressing change (3 patients in SecurAcath® and 10 patients in StatLock® group). We repeated the analysis assuming four dressing changes per patient. Data were simulated with parameters obtained from the linear mixed model on the observed log-transformed data. For the fixed effect (i.e. the difference between both groups) various settings were explored. Specific interest was in the worst case scenarios where the time needed for dressing change was longer in the SecurAcath® group, as opposed to the observed data. Within each considered scenario, data were simulated for the patients with missing data and the analysis was performed on the total dataset (105 patients). For each scenario, this was repeated 100 times and the mean (backtransformed from the log-scale) % reduction in time with SecurAcath® and its 95% confidence interval was calculated.

Figure 5: Sensitivity analysis
Caption Figure 5: Mean (backtransformed from the log-scale) % reduction in time with SecurAcath® and its 95%confidence interval obtained for various scenarios for the ratio SecurAcath® /StatLock® within the group of missing patients. The left solid vertical line refers to the observed ratio (ratio=0.59, i.e. 41% reduction). The right solid line, the ratio which needs to be assumed for the patients with missing data in order to obtain a non-significant difference between both groups.

The p-values values are 1 only when the distributions of the two samples for instance are identical - I could not see that was the case.

Response: We understand the point of the reviewer, however we disagree at this point. Let’s try to explain our point here below.
When an exact test is performed involving discrete data, it is not a necessary condition that the distribution in the two samples is identical in order to obtain a p-value equal to zero. I invite the reviewer to verify the simple setting comparing the proportion between two groups using a Fisher's exact test. When the proportion equals 1/50 in group 1 and 1/100 in group 2, the exact P-value of the Fisher's exact test equals 1. The following SAS macro illustrates this:”

```
%macro showpvalue;
 /*Binary data. Two groups. One event in each group. Sample size in group 2 is 100.
 Sample size in group 1 varies from 1 to 100. Result Fisher's exact test is reported*/
data all;set _null_;run;
%do i=1 %to 99 %by 1;
 ods select none;
```

```
 data input;
 group=1; y=0; n=&i;output;
 group=1; y=1; n=1;output;
 group=2; y=0; n=99;output;
 group=2; y=1; n=1;output;
 run;
 proc freq data=input;tables group*y;weight n;exact or fisher;
 ods output FishersExact=fisher;run;
 data fisher;set fisher;n_group1=1+&i;where name1="XP2_FISH";run;
 data all;set all fisher;run;
%end;
ods select all;
proc print data=all label noobs;
 var n_group1 nvalue1;
 format nvalue1 20.13;
 label n_group1="Sample size in group 1";
run;
%mend;
%showpvalue;
```

VERSION 3 – REVIEW

REVIEWER	Dr Irina Chis Ster St George's University of London
REVIEW RETURNED	27-Oct-2017

GENERAL COMMENTS	The authors acceptably addressed the attrition issue. The chi-squared tests presented in Table 3, however, are invalid as they violate observations' independence. I can see more than one "problem during dressing change" per patient and chi-squared can account for the two sources of variability in the data - within patient and between patients. One solution to that is to lump "the problems during dressing" change all together and employ a two-level logistic regression on this binary outcome. Of course, breaking them down by their type, may be of clinical interest. But the statistical tests as they are presented now are incorrectly applied.

VERSION 3 – AUTHOR RESPONSE

We thank the reviewer for her important remark because, indeed the reviewer was absolutely right that the p-values in Table 3 were a simplification since they ignored the correlation between the multiple dressing changes of the same patient. Therefore, we replaced the chi^2 test comparing the proportion of dressing changes where a problem occurred by a logistic regression with generalised estimating equations (GEE) based on an independent working correlation matrix to handle the correlation between the multiple dressing changes within the same patient. Since approaches to handle the correlation between multiple events rely on asymptotics, it was not appropriate to use the same strategy for all specific problems (since the number of events was low to extremely low). Therefore, we deemed it more meaningful to refrain from reporting results from statistical tests for the comparison of the specific problems and only give descriptive information.

VERSION 4 – REVIEW

REVIEWER	Irina Chis Ster St George's University of London
REVIEW RETURNED	07-Dec-2017

GENERAL COMMENTS	The authors replied adequately to my latest queries.